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## Histopathology of Conjunctivochalasis Compared to Normal Conjunctiva

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### Abstract

**Purpose:** To evaluate the histopathologic changes in the conjunctiva of patients with conjunctivochalasis (CCh) compared to age-matched controls.

**Methods:** This cross-sectional, controlled study included 27 eyes of 27 patients with CCh and 16 eyes of 16 age-matched controls. A biopsy of the bulbar conjunctiva was performed along the temporal lower lid margin before cataract surgery in both groups. Histopathologic evaluation of the specimens was done with light microscopy using staining with hematoxylin/eosin, periodic acid Schiff, and van Gieson elastic stain. Various histopathologic features of the conjunctival epithelium and stroma were compared between the two groups.

**Results:** The mean age of patients was  $62.4 \pm 6.9$  years in the CCh group and  $65.1 \pm 6.3$  years in the control group ( $P = 0.54$ ). No significant differences were noted between the two groups in terms of conjunctival epithelial changes including papillomatosis, epithelial clefts, epithelial goblet cells, or infiltration of inflammatory cells. Mean thickness of the conjunctival stroma was  $0.21 \pm 0.08$  mm in the CCh group and  $0.26 \pm 0.21$  mm in the control group ( $P = 0.10$ ). For the conjunctival stroma, there were no significant differences between the two groups in terms of elastosis, fibrosis, lymphangiectasia, or infiltration of inflammatory cells.

**Conclusion:** No noticeable differences were found in the histopathologic features by light microscopy between eyes with CCh and those of age-matched controls. Therefore, the primary pathology of CCh may not be within the conjunctiva itself. Instead, loose attachment of the conjunctiva to the underlying tissue may be the reason for the redundant folds in the bulbar conjunctiva.

**Keywords:** Conjunctiva; Conjunctivochalasis; Histopathology; Tenon's Capsule

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## INTRODUCTION

Conjunctivochalasis (CCh), defined as a redundant, loose, non-edematous bulbar conjunctiva interposed between the globe and the eyelid, tends to be bilateral and is more prevalent in the inferior bulbar conjunctiva.<sup>[1-3]</sup>

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Conjunctivochalasis is generally considered a condition of the older population; a large community-based epidemiological study estimated a prevalence rate of 44.8% in people over 60 years of age.<sup>[4]</sup> Furthermore, the disease severity increases with age.<sup>[4,5]</sup> Conjunctivochalasis is a very important and often overlooked cause of ocular discomfort, associated with various symptoms such as irritation, epiphora, dryness, and blurred vision.<sup>[2,6,7]</sup> Mild CCh causes and aggravates an unstable tear film by depleting the tear meniscus; moderate CCh causes intermittent epiphora by interfering with tear clearance; and severe CCh causes exposure-related problems such as nocturnal lagophthalmos and dellen formation.<sup>[3]</sup>

Despite its high prevalence among the elderly, the exact pathogenesis of CCh remains to be elucidated. In addition, the histopathologic data on CCh are scanty and conflicting.<sup>[3,8]</sup> Although certain conjunctival changes including fragmentation or reduced number of elastic fibers,<sup>[2,9,10]</sup> lymphangiectasia,<sup>[9]</sup> or chronic inflammation<sup>[10,11]</sup> have been described in some reports, these have not been confirmed by other studies.<sup>[7,11,12]</sup>

Therefore, to shed light on the structural changes in CCh, this study was designed to evaluate histopathologic changes in the conjunctiva of eyes with CCh compared to an age-matched control group.

## METHODS

This cross-sectional, controlled study included 27 eyes of 27 patients with CCh as the study group and 16 eyes of 16 age-matched patients without CCh as the control group. Protocol of the study was approved by the Institutional Review Board of Farabi Eye Hospital, Tehran, Iran.

All patients in both CCh and control groups were consecutively selected from individuals who were candidates for cataract surgery, regardless of symptoms of ocular irritation. Based on the presence or absence of CCh, these cases were assigned to the CCh group or the control group, respectively. Diagnosis of CCh was based on the clinical examination showing the presence of redundant bulbar conjunctival folds along the temporal lower lid margin. All patients also underwent slit lamp photography with and without fluorescein staining; the former demonstrated typical undulations in the inferotemporal tear meniscus. Patients in the control group did not show redundant conjunctival folds in any part of the bulbar conjunctiva and they had continuous uninterrupted tear menisci along the upper and lower lid margins. Exclusion criteria in both groups included any form of conjunctival or ocular inflammation, untreated dry eye disease, meibomian gland dysfunction, blepharitis, pterygium or pingueculum, a history of contact lens wear, use of any topical medications except for non-preserved artificial tears, and any previous ocular surgery. After full explanation of the purpose of the study, all patients consented to participate in this study.

Just before starting cataract surgery, all patients in both groups underwent a conjunctival biopsy under topical anesthesia. The biopsy included a 2 × 2-mm strip of the bulbar conjunctiva along the temporal lower lid margin starting at 1 mm posterior to the limbus. The area was then left bare and the patient subsequently underwent a routine temporal - approach phacoemulsification surgery with a clear corneal incision.

After immediate fixation, all conjunctiva specimens were sent for histopathologic examinations. An ocular pathologist (MM), who was masked to the clinical diagnosis of each patient, evaluated all specimens. Specimens were stained with hematoxylin/eosin (H/E), periodic acid Schiff (PAS), and van Gieson elastic stain.

To allow statistical comparisons between the two groups, a semi-quantitative scoring system was used for histopathologic parameters [Table 1]. The following histopathologic parameters were evaluated in conjunctival specimens: epithelial papillomatosis, epithelial clefts, epithelial goblet cells, epithelial infiltration of inflammatory cells, stromal thickness, stromal elastosis, stromal fibrosis, stromal lymphangiectasia, and stromal infiltration of inflammatory cells. Chi square test and *t*-test were used for comparison of the parameters between the CCh group and the control group. *P* values of less than 0.05 were considered as statistically significant.

## RESULTS

The CCh group included 27 eyes of 27 patients (18 men and 9 women) with a mean age of  $62.4 \pm 6.9$  years (range, 50–76 years). The control group comprised of 16 eyes of 16 patients (11 men and 5 women) with a mean age of  $65.1 \pm 6.3$  years (range, 52–71 years). There was no statistically significant difference in the age between the two groups (*P* = 0.54).

Details of histopathologic findings in eyes with CCh and the controls have been shown in Table 2. No significant differences were noted between the two groups regarding the conjunctival epithelial changes, including papillomatosis, epithelial clefts, epithelial goblet cells, and infiltration of inflammatory cells.

Mean thickness of the conjunctival stroma was  $0.21 \pm 0.08$  mm in the CCh group and  $0.26 \pm 0.21$  mm in the control group (*P* = 0.10). Evaluation of the conjunctival stroma revealed no significant differences between the two groups in terms of elastosis or fibrosis [Table 2]. Different degrees of stromal lymphangiectasia were observed in 19 eyes (70.1%) of the CCh group and in 7 eyes (43.8%) of the control group; however, the difference was not statistically significant (*P* = 0.21). Furthermore, infiltration of inflammatory cells in the conjunctival stroma was noted in 8 eyes (29.6%) of the CCh group (including 7 eyes with mild infiltration and 1 eye with moderate infiltration) and in 2 eyes (12.5%)

**Table 1. Scoring system for various histopathologic parameters in the conjunctival epithelium and stroma using light microscopy**

	Score 0	Score 1	Score 2	Score 3
<b>Conjunctival Epithelial Changes</b>				
Epithelial papillomatosis	Not significant	Mild	Moderate	Severe
Epithelial clefts	Negative	<1/HPF	1-2/HPF	>2/HPF
Epithelial goblet cells	Negative	<1/HPF	1-3/HPF	>3/HPF
Epithelial infiltration of inflammatory cells	Negative	Mild	Moderate	Severe
<b>Conjunctival Stromal Changes</b>				
Stromal elastosis	Negative	<3%	3-10%	>10%
Stromal fibrosis	Rare, patchy (<10%)	Occasional, patchy (10-50%)	Diffuse (>50%)	
Stromal lymphangiectasia	<10%	10-50%	>50%	
Stromal infiltration of inflammatory cells	Few cells throughout the tissue	Patchy increased, <1 focus/HPF	Patchy increased, ≥1 focus/HPF	Diffusely increased

HPF, high power field

**Table 2. Comparison of various histopathologic parameters of conjunctiva between eyes with conjunctivochalasis and those of age-matched controls**

	Conjunctivochalasis (n=27)				Normal Conjunctiva (n=16)				P
	Score 0	Score 1	Score 2	Score 3	Score 0	Score 1	Score 2	Score 3	
Epithelial papillomatosis	17	9	1	0	14	2	0	0	0.20
Epithelial clefts	20	7	0	0	14	2	0	0	0.29
Epithelial goblet cells	3	21	3	0	4	9	3	0	0.32
Epithelial infiltration of inflammatory cells	6	19	2	0	4	12	0	0	0.53
Stromal elastosis	11	11	5	0	8	8	0	0	0.28
Stromal fibrosis	15	10	2		10	6	0		0.53
Stromal lymphangiectasia	8	15	4		9	6	1		0.21
Stromal infiltration of inflammatory cells	19	7	1	0	14	2	0	0	0.39

of the control group (both with mild infiltration). There was no statistically significant difference in inflammatory cell infiltration of the conjunctival stroma between the two groups ( $P = 0.39$ ).

## DISCUSSION

In this cross-sectional, controlled study using light microscopy, there were no significant differences in various histopathologic parameters of the conjunctival epithelium and stroma between eyes with CCh and those of age-matched controls. This may signify that in eyes with CCh the conjunctiva may be structurally normal and the loose, redundant folds may indeed be due to the loss of adhesion of this structurally normal conjunctiva to the underlying tissue.

Despite the high prevalence of CCh, particularly among elderly,<sup>[4,5]</sup> the exact mechanisms involved in its pathogenesis remain unknown. To elucidate the pathogenesis, it is critical to have a clear understanding of the histopathologic changes in this common disease. However, the few published reports<sup>[1,2,7,9-12]</sup> on the

CCh histopathology have reported conflicting results and suffer from notable limitations such as a lack of age-matched controls,<sup>[9]</sup> or a very small sample size.<sup>[1,2,7]</sup> In addition, in other studies,<sup>[10-12]</sup> the histopathologic findings in CCh and control groups have been expressed descriptively and no quantitative or even semi-quantitative scoring has been used to compare these changes. To address these limitations, we have included a relatively notable sample size of CCh eyes as well as age-matched controls. Furthermore, a semi-quantitative scoring system [Table 1] was employed to allow a better comparison between the two groups.

Using light microscopy and the above-mentioned scoring system in this study, there were no significant differences between the CCh group and the controls regarding the conjunctival epithelial changes [Table 2]. Although using light microscopy, a normal conjunctival epithelium has been reported in some previous studies,<sup>[2,9]</sup> epithelial abnormalities, such as hyperplasia, have been noted in others.<sup>[10]</sup> In addition, using transmission electron microscopy, a decreased epithelial cohesiveness was observed by Ward et al.<sup>[12]</sup> In fact, these epithelial

changes in CCh may be secondary to the altered tear distribution and increased friction rather than due to a primary change in CCh.

Even though eyes with CCh in this study showed lower values of stromal thickness than the controls ( $0.21 \pm 0.08$  mm versus  $0.26 \pm 0.21$  mm, respectively), the difference was not statistically significant ( $P = 0.10$ ). Using optical coherence tomography (OCT) of lower temporal conjunctiva 3–5 mm from the limbus, Zhang et al demonstrated a significantly lower thickness of the conjunctiva in eyes with CCh ( $195.6 \pm 25.7$   $\mu$ m) compared to the age-matched controls ( $215.8 \pm 35$   $\mu$ m).<sup>[13]</sup> However, because the posterior border of the conjunctival stroma cannot be clearly distinguished from the underlying tissues in OCT,<sup>[14]</sup> the histopathologic measurements are more accurate for this purpose.

In our study there were no significant differences between the two groups in terms of fibrosis or elastosis in the conjunctival stroma, as has been reported in a previous study.<sup>[1]</sup> Nevertheless, abnormalities of elastic fibers, such as fragmentation,<sup>[2,9]</sup> accumulation,<sup>[12]</sup> or reduced number,<sup>[10]</sup> have been previously described by others. Similar to our results, in a study by Francis et al on 18 patients with CCh (29 biopsy specimens) and 24 controls (24 biopsy specimens), 22 of 29 specimens of CCh (76%) had normal conjunctiva, and only three of their specimens demonstrated stromal elastosis.<sup>[11]</sup> The spectrum of these contradictory changes may be due to the grade of disease severity, location of the conjunctival biopsy, or the degree of actinic damage.<sup>[15]</sup> On the other hand, although in our study lymphangiectasia was more common in the CCh group (70.1% versus 43.8%), the difference did not reach statistical significance [Table 2]. Lymphangiectasia in these cases has been attributed to an edematous artifact in the subepithelial tissue of the conjunctiva.<sup>[16]</sup>

Similar to previous studies,<sup>[7,9-12]</sup> in the current study there was no significant difference in infiltration of the inflammatory cells in the conjunctiva of those with CCh compared to the control group. However, inflammation has been suggested to play a role in the pathogenesis of CCh by showing an increased level of proinflammatory cytokines in tear film of these cases.<sup>[12,17,18]</sup> Such an increased level of inflammatory cytokines may have originated from conjunctival epithelium due to the mechanical friction of the conjunctival folds during the blinking.<sup>[12]</sup> In addition, increased levels of matrix metalloproteinase and the resultant collagenolytic activity<sup>[19]</sup> as well as the presence of conjunctival oxidative stress, evidenced by positive staining for markers of lipid peroxidation and the DNA damage,<sup>[12]</sup> have been suggested to play a role in formation of CCh.

The lack of any significant difference in light microscopy findings between eyes with CCh and those of age-matched controls in this study may suggest that the conjunctiva may not be the primary location

of the pathogenetic process in CCh. Instead, the loose attachment of the conjunctiva to the underlying sclera may be the mechanism which results in development of the redundant conjunctival folds. This concept is being supported by the fact that dissolution of the Tenon's capsule has been noted intraoperatively in eyes with CCh.<sup>[20,21]</sup> On the other hand, the surgical procedures which create tight adhesion of the conjunctiva to the underlying sclera, even without conjunctival resection, have been shown to result in significant improvement of symptoms and signs of CCh.<sup>[22]</sup> Therefore, future studies are required to evaluate the involvement of conjunctiva-Tenon's capsule-sclera complex in CCh, particularly the adhesion between structures in this complex.

Our study was cross-sectional with an age-matched control group. An arbitrary scoring system was used in this study to make it possible to compare various histopathologic parameters in the conjunctival epithelium and stroma between the groups. However, because of the limitations of light microscopy, the exact quantification of parameters was not performed in this study. On the other hand, this study included patients with CCh regardless of their symptoms or degree of CCh severity. It might be possible to observe different histopathologic changes in symptomatic eyes with severe CCh than those with mild or asymptomatic disease. With all these limitations in mind, our study showed that there are no significant differences in histopathologic changes, as detected by light microscopy, in eyes with CCh and those of age-matched controls. Loose adhesion of the conjunctiva to the underlying tissues may be the reason for formation of the redundant conjunctival folds.

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Nil.

## Conflicts of Interest

There are no conflicts of interest.

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